REMARKS

Claims 1-4 were pending. Claim 2 has been amended. Claim 3 has been canceled. Claims 1 and 4 have been withdrawn from consideration as drawn to non-elected subject matter. Upon entry of these amendments claim 2 is pending and under consideration.

I. CLAIM AMENDMENTS

Claim 2 has been amended to eliminate the reference to the terms "controlling" and "controls" objected to by the Examiner and to define the peptide complex of the claimed method. Additionally, claim 2 has been amended to specify the effect of an agent on calcium ion concentration in the HepG2 cell. Support for these amendments can be found, for example, on page 2, paragraph 8 of the instant specification and in the original claims 3 and 4. Accordingly, these amendments do not introduce new matter. Entry thereof is respectfully requested.

II. THE REJECTION UNDER 35 USC § 112, 2nd PARAGRAPH

Claims 2 and 3 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that claim 2 is indefinite in that the recitation of "controlling" and "controls" fails to indicate whether the movement of the claimed complex is inhibited or catalyzed and whether the agent increases or decreases the calcium ion concentration, respectively. Reconsideration is respectfully requested in view of the amendments made to claim 2.

Applicants have amended claim 2 to eliminate the language objected to by the Examiner to recite: "A method for promoting movement of Hepatitis B virus polymerase (HBVPol) /11 kDa Ca^{2+} binding protein p11 complex into the nucleus of a HepG2 cell through adjustment of the intracellular concentration of Ca^{2+} ion by administrating an agent which decreases the calcium ion concentration in the HepG2 cell." As amended, claim 2 defines the method of promoting movement of the peptide complex into the nucleus of a HepG2 cell and specifies that the agent decreases calcium ion concentration in the target cell. Therefore, Claim 2 is definite.

Claim 3 has been canceled without prejudice rendering the rejection moot with respect to this claim.

Accordingly, it is respectfully requested that the rejection of claims 2 and 3 under 35 U.S.C. §112, second paragraph, be withdrawn.

III. REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH

Claims 2 and 3 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement by containing subject matter which was not described in the specification in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/or use the invention without undue experimentation. In particular, the Examiner alleges that the teachings of the instant specification contradict the state of the art at the time the application was filed in that the increasing intracellular calcium, for example, by valinomycin, prevents the movement of the HBVPol/p11 complex into the nucleus and, therefore, the skilled artisan would have to invest undue experimentation in order to make and use the claimed invention. This rejection is traversed. Reconsideration is respectfully requested.

A claim is enabled if one skilled in the art, guided by Applicant's disclosure, can make and use the claimed invention without undue experimentation. *See In re Wands* 8USPQ2d 1400, 1404 (Fed. Cir. 1988). Although the Examiner referred to *In re Wands*, he merely listed the factors to be considered in determining whether a disclosure would require undue experimentation and provided no discussion of any of these factors which must be proven to make a case of non-enablement. Applicants respectfully submit that the initial burden is on the Office to provide evidence of non-enablement for each of these factors. *See* M.P.E.P. at §§ 2164.01(a); 2164.04. In the absence of evidence from the PTO, each of these factors favors enablement of the rejected claims.

Nevertheless, in order to expedite prosecution, Applicants offer the following arguments and respectfully submit that the instant disclosure is enabling for practicing a method for promoting movement of Hepatitis B virus polymerase/Ca^{2+} binding protein complex into the nucleus of a HepG2 cell as instantly claimed without undue experimentation.

The instant specification provides an ample disclosure of all of the elements of the claimed method. The protein complex to be used in accordance with the claimed method is fully enabled by the instant specification, including the Hepatitis B virus polymerase (HBVPol), 11kDa Ca^{2+} binding protein (p11) and the conditions promoting movement of the protein complex into the nucleus of a HepG2 cell (see, *e.g.*, paragraphs 0006, 0008 on pages

2-3, paragraphs 0017-0019, 0024 on pages 3-4 and paragraphs 0059-0060 on page 11 of the specification). The corresponding disclosure (specifically, paragraphs 0024 and 0059-0060) teaches that the movement of the HBVPol/p11 complex into the nucleus of a HepG2 cell can be modulated by calcium ion concentration in the cell. Thus, when p11 is treated with a calcium blocker (*e.g.*, EGTA; see, paragraph 0059), the protein complex migrates to the nucleus of the cell. In the instance when p11 is treated with an agent capable of increasing calcium ion concentration (*e.g.*, valinomycin; see, paragraph 0059), the peptide complex remains in the cytoplasm of the cell. Accordingly, p11 plays an important role in the process of migration of the peptide complex into the nucleus of a HepG2 cell.

In this regard, the Examiner's allegation that the teachings of the instant specification contradict the state of the art at the time the application was filed in that the increasing intracellular calcium, for example, by valinomycin, prevents the movement of the HBVPol/p11 complex into the nucleus, is irrelevant. The art cited by the Examiner refers to the HBV polymerase, not to the HBVPol/p11 complex. As noted above, p11 plays an important role in the process of migration of the peptide complex into the nucleus of the cell. Accordingly, the results obtained in the absence of p11 cannot be interpreted as comparable with those performed in the presence of this component. Therefore, the teachings of the instant specification do not contradict the state of the art at the time the application was filed.

Based on aforementioned, Applicants respectfully submit that the instant specification provides sufficient guidance and is fully enabling for a skilled artisan to make and use the method for promoting movement of Hepatitis B virus polymerase/Ca^{2+} binding protein complex into the nucleus of a HepG2 cell as instantly claimed without undue experimentation. "The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art." *See*, MPEP § 2140. Thus, the enablement requirement is satisfied. It is respectfully requested that rejection of claims 2 and 3 under 35 U.S.C. §112, first paragraph, be withdrawn.

IV. REJECTION UNDER 35 U.S.C. §102

Claims 2 and 3 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Schneider *et al.* (US 2002/0045191, hereinafter "Schneider"). In particular, the Examiner is of the opinion that as Schneider discloses treating of HBV-infected HepGe cells with

valinomycin, the reference anticipates the subject matter of claims 2 and 3. This rejection is traversed. Reconsideration is respectfully requested.

It is well established law that every limitation of a claim must appear in a single prior art reference for it to anticipate the claim. *Gechter v. Davidson* 116 F.3d 1454, 43 USPQ2d 1030 (Fed. Cir. 1997). It is respectfully submitted that Schneider does not disclose each and every element of claims 2 and 3, as explained below.

As discussed in Section III above, the present invention relates to a method of promoting movement of a Hepatitis B virus polymerase (HBVPol)/11 kDa calcium binding protein (p11) complex into the nucleus of a HepG2 cell. This movement is promoted by decrease in the concentration of calcium ions in the target cell, as recited in amended claim 2. In contrast, Schneider discloses a method of treating an HBV-infected HepG2 cell with valinomycin, the agent well known to <u>increase</u> intracellular concentration of calcium ions. Thus, not only is the HBVPol/p11 peptide complex of the claimed method distinct from HBV disclosed by Schneider, the conditions employed by the both methods are completely different. As such, Schneider does not teach each and every limitation of the claimed method and, therefore, cannot anticipate claim 2.

Claim 3 is canceled without prejudice rendering the rejection moot with respect to this claim.

Accordingly, it is respectfully requested that the rejection of claims 2 and 3 under 35 U.S.C. §102(e) be withdrawn.

CONCLUSION

Applicants respectfully submit that claim 2 satisfies all the criteria for patentability and is in condition for allowance. An early indication thereof is respectfully solicited.

No fee is believed to be due with this submission. However, should any fee be required, the Commissioner is authorized to charge all required fees or credit any overpayment, to Jones Day U.S. Deposit Account No. 503013, referencing Attorney Docket No. 8111-032-999.

Respectfully submitted,

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